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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,877	02/02/2005	Takehiko Nomura	0020-5340PUS1	5247

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EXAMINER
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MACAULEY, SHERIDAN R

ART UNIT	PAPER NUMBER
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1651

NOTIFICATION DATE	DELIVERY MODE
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01/27/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/522,877	<b>Applicant(s)</b> NOMURA ET AL.	
	<b>Examiner</b> SHERIDAN R. MACAULEY	<b>Art Unit</b> 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 02 December 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 6, 14, 18 and 41-47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 6, 14, 18 and 41-47 is/are rejected.
- 7) ☒ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/2/2008</u> .   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

A response and amendment were received and entered on November 7, 2008. All evidence and arguments have been fully considered. Claim 11 was cancelled. Claims 6, 14, 18 and 41-47 are pending.

#### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 7, 2003 has been entered.

#### ***Declaration under 37 CFR 1.132***

2. The declaration under 37 CFR 1.132 filed November 7, 2008 is insufficient to overcome the rejection of claims 6, 14, 18 and 41-47 based upon 35 USC 103 as set forth in the last Office action because the evidence and arguments presented in the declaration are not commensurate in scope with the claims. Applicant presents evidence suggesting that the improved composition can be achieved by using an organic solvent of 10% ethanol in heptane, whereas the instant claims are directed to a composition prepared using an organic solvent that is hexane or heptane that comprises 5 to 20% (v/v) of ethanol. Further, although the declaration presents

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evidence suggesting that one of ordinary skill in the art would not have been able to prepare the claimed composition using the teachings of the prior art, this has not been found to be persuasive. As discussed below and in the prior art, one of ordinary skill in the art would have had a reasonable expectation of success in preparing a composition with the claimed particle sizes and viscosity. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

### ***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 6, 14, 18 and 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Azuma (EP 1097715 A1, cited in prior action) in view of Van Nest et al. (EP 0399843 A2). Claim 6 recites a paste comprising Bacillus Calmette-Guerin – cell wall Skeleton (BCG-CWS), wherein the paste comprises 6.6 g to 35.2 g of squalane per about 0.67 g of BCG-CWS and has the following properties: (1) a viscosity between 0.2 and 0.7 poise at 25 degrees C, (2) comprising an assembly of BCG-CWS particles, wherein the particle diameter is from 0.1 microns to 20 microns in the particle size distribution and showing a single peak distribution with D10%:  $0.23 \pm 0.05$  microns and D90%:  $0.60 \pm 0.05$  microns, and (3) obtained by a process for preparation which comprises the following steps: (a) mixing the BCG-CWS and squalane in an organic solvent that is hexane or heptane which comprises 5 to 20 (v/v) ethanol; and (b) a step of removing the organic solvent by distillation. Claim 14 recites the paste according to claim 1 that is formulated as an oil-in-water emulsion, which comprises 0.66 g of the BCG-CWS, 0.4 wt% to 8 wt% of the squalane, 0.01 to 3% of polyethylenesorbital fatty acid ester and 1 to 10% of mannitol per 2L of water. Claim 18 recites the paste according to claim 17, wherein the polyethylenesorbital fatty acid ester is TWEEN 80 (polysorbate 80). Claims 41 and 42 recite a pharmaceutical composition comprising

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the emulsion according to claim 14 or 6. Claims 43 and 44 recite the paste of claim 6 wherein the paste has a viscosity of between 0.43 and 0.55 poise, specifically 0.43, at 25 degrees C. Claim 45 recites the paste according to claim 6 where the paste comprises 8.9 to 17.9 g of squalane per about 0.67 g of BCG-CWS. Claim 46 recites a paste comprising BCG-CWS and squalane, wherein the weight squalane : weight BCG CWS of said paste is 9.8 to 52.5, and wherein the viscosity of said paste is between 0.2 and 0.7 poise at 25 degrees C. Claim 47 recites the paste of claim 46, formulated as an assembly of BCG-CWS particles, wherein the particles have a diameter of between 0.1 microns to 20 microns and has a single peak of particle size distribution with D10%:  $0.23 \pm 0.05$  microns and D90%:  $0.60 \pm 0.05$  microns.

7. Azuma teaches a paste comprising bacterial CWS (including BCG-CWS, i.e. CWS from the BCG strain of *Mycobacterium bovis*) and an oil (squalane). Although Azuma does not disclose the viscosity of the paste, it is made by nearly identical methods to those described in the instant application (p. 17, line 57-p. 18, line 5). The paste of Azuma would therefore inherently have a viscosity within the disclosed range. Azuma teaches that the particle diameter of the droplets is from 0.1 to 20 microns (p. 3, lines 10-18, p. 4, lines 6-14 and p. 6, lines 13-17). Azuma teaches that the paste is formulated as an assembly of bacterial CWS particles, and that the paste is formulated as an oil-in-water emulsion (p. 4, lines 4-22). Azuma et al. teaches that the emulsion can be used as a pharmaceutical composition (p. 8, lines 51-53). Azuma teaches that the composition may comprise 0.2% TWEEN 80 (i.e., polysorbate 80), 2.3% mannitol, about 1.6 weight% of oil and water (p. 10, lines 1-8, table 1). Azuma teaches that the

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compositions may comprise between about 1 g of bacterial CWS per 2 liters of water (p. 10, lines 1-8). Azuma also teaches that a composition with a single peak for particle size is preferable because it is indicative of stability of the composition (p. 6, lines 18-23).

8. Azuma does not specifically teach a composition comprising all of the claimed ratios of BCG-CWS to squalane, or a composition wherein the particle size distribution shows a single peak as well as D10%:  $0.23 \pm 0.05$  microns and D90%:  $0.60 \pm 0.05$  microns.

9. Van Nest teaches a composition which is an oil-in-water emulsion comprising a muramyl dipeptide derivative (MTP-PE, see p. 2, lines 41-55) and an oil, wherein the particle size is less than one micron, specifically between 0.5 and 0.8 microns (p. 24, lines 25-42). Van Nest teaches that reducing oil droplet size improves the adjuvant performance (p. 24, lines 41-42). Van Nest teaches a method of reducing oil droplet size in the composition (p. 7, lines 12-22).

10. At the time of the invention, a composition comprising nearly all of the claimed elements was known, as taught by Azuma. Although Azuma does not disclose the viscosity of the paste, it is made by nearly identical methods to those described in the instant application (p. 17, line 57-p. 18, line 5). The paste of Azuma would therefore be expected to have a viscosity within the disclosed range. It was also known at the time of the invention that the particle size of oil-in-water compositions comprising similar components could be reduced within the claimed range, and that compositions comprising a single peak for particle size distribution are preferential, as taught by Van

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Nest and Azuma, respectively. One of ordinary skill in the art would have been motivated to reduce the particle size of the oil-in-water emulsion of Azuma to the range taught by Van Nest because Van Nest teaches that the reduced droplet size improves the performance of the compound as an adjuvant. Furthermore, Azuma teaches that the amount of squalane in the compositions may be varied to produce the desired effect (p. 5, par. 20); one of ordinary skill in the art would therefore have been motivated to modify the ratio of BCG-CWS to squalane in the course of routine experimentation, and could have done so with a reasonable expectation of success. One would have a reasonable expectation of success in reducing droplet size because methods to reduce droplet size were successfully employed by Van Nest using a similar composition. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

11. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

### ***Response to Arguments***

12. Applicant's arguments filed November 7, 2008 have been fully considered but they are not persuasive. Applicant argues that the teachings of Azuma and Van Nest could not have been used at the time of the invention to arrive at the claimed composition, that the references do not teach the specific emulsifying steps recited in the instant claims, and argument that the claimed invention is not obvious in view of



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the teachings of the prior art because the instant invention presents an unexpected advantage.

13. In response to applicant's argument that the teachings of Azuma and Van Nest could not have been used at the time of the invention to arrive at the claimed composition, it is noted that the Azuma and Van Nest references are both directed to the production of oil in water emulsions comprising bacterial cell walls (see Azuma, abstract, and Van Nest, p. 7, lines 38-47). Although applicant argues that the methods of Van Nest could not be used to arrive at the claimed composition because Van Nest is directed to compositions that comprise more cell wall components than those of Van Nest, this is not found to be persuasive because Van Nest teaches the preparation of compositions comprising killed bacterial cells (p. 7, lines 44-45), which comprise all cell wall components. Applicant's assertion that Van Nest does not provide enough direction to enable one of ordinary skill in the art to arrive at the claimed particle distribution using BCG-CWS is not found persuasive because Van Nest teaches several methods by which one of ordinary skill in the art may reduce droplet size in a variety of emulsions, as discussed above, and that such methods are common in the art; thus, Van Nest provides evidence that one of ordinary skill in the art would have been able to prepare the claimed composition using the teachings of the prior art at the time of the invention. Van Nest further teaches the desirability for the use of cell wall components from killed cells, which is also taught to be desirable by Azuma. One of ordinary skill in the art would have recognized that the teachings of Van Nest could have been applied to the preparation of BCG-CWS because Van Nest teaches that reduced particle size in an oil-

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in-water emulsion such as the one taught by Azuma improves the performance of the compound as an adjuvant. One of ordinary skill in the art would therefore have recognized that the teachings of Van Nest would have been applicable to the modification of the oil in water emulsions of Azuma, and would have had a reasonable expectation of success in applying the techniques of Van Nest to the compositions of Azuma.

14. In response to applicant's argument that the references do not teach the specific emulsifying steps recited in the instant claims, it is noted that the claims recite a product claim that is defined in terms of the process by which it is made. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps (MPEP 2113). As discussed above, there does not appear to be an unobvious difference between the claimed product and that of the prior art. Therefore, the claimed product is rendered obvious by the teachings of the prior art.

15. In response to applicant's argument that the claimed invention is not obvious in view of the teachings of the prior art because the instant invention presents an unexpected advantage, it is noted that the evidence and arguments presented to demonstrate unexpected results are not commensurate in scope with the claims. Applicant presents evidence suggesting that the improved composition can be achieved by using an organic solvent of 10% ethanol in heptane, whereas the instant claims are directed to a composition prepared using an organic solvent that is hexane or heptane that comprises 5 to 20% (v/v) of ethanol. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims.

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16. Therefore, applicant's arguments have been fully considered, but they have not been found to be persuasive.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHERIDAN R. MACAULEY whose telephone number is (571)270-3056. The examiner can normally be reached on Mon-Thurs, 7:30AM-5:00PM EST, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SRM

/Ruth A. Davis/  
Primary Examiner, Art Unit 1651